Adenomas involving the extrahepatic biliary tree are rare but have an aggressive clinical course

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Biliary adenomas that are usually found in surgically removed gallbladders are rare, but can also occur in the extrahepatic biliary tree. We present a case series of extrahepatic bile duct adenomas at our institution, along with a review of the literature. All three patients with extrahepatic biliary adenomas (two in the common bile ducts, one in the hepatic duct) were female with a mean age of 74 years. On initial presentation, none of the patients had obstructive jaundice but two of the three patients had symptoms of biliary origin. Case 1 is an 85-year-old woman with an incidental biliary dilation seen on chest imaging; endoscopic ultrasound revealed a sessile adenomatous polyp in the distal bile duct. The patient refused surgery and presented with occlusive biliary stricture and jaundice 5 months after initial presentation, with cytology confirming malignant progression. Case 2 is a 78-year-old woman with a history of primary sclerosing cholangitis and who presented with cholangitis, and Gram-negative sepsis. A polypoid lesion was seen on imaging in the common hepatic duct and direct cholangioscopy with biopsies confirmed the presence of adenoma with high grade dysplasia. The patient underwent successful total bile duct resection and hepaticojejunostomy but represented 1 year later with diffuse metastatic disease to the bone, liver, and peritoneum. Case 3 is a 61-year-old woman who presented with symptoms suggestive of gallbladder pathology and was found to have a polypoid bile duct lesion on intraoperative cholangiogram. Endoscopic retrograde cholangioscopy showed an adenomatous polyp with high grade dysplasia involving the distal common bile duct. The patient underwent distal bile duct resection with choledochojejunostomy but presented with jaundice 4 years after surgery. She was found to have adenocarcinoma involving the small bowel in the Roux limb of jejunum and transverse colon. All three patients in our series presented with interval gastrointestinal malignancy and we therefore recommend aggressive surgical intervention and close postoperative surveillance when diagnosis of extrahepatic bile duct adenoma is made.

Introduction

Biliary adenomas are rare entities that are usually detected incidentally in gallbladders removed for cholelithiasis or chronic cholecystitis. They can also occur anywhere in the extrahepatic biliary tree. There is limited understanding of the malignant potential of adenomas involving the extrahepatic biliary tree, and there are no guidelines for management. The aim of our study was to identify all extrahepatic biliary adenomas diagnosed at our tertiary care institution, and review their management and clinical outcomes. In addition, we present a literature review of published cases of extrahepatic biliary adenoma.

Methods

We used the pathology database (CoPath) at our institution to identify patients with a diagnosis of biliary adenoma or adenomatous change on biopsy or surgical resection specimens from year 2000 to 2013. Pathology results from 8774 cholecystectomies (with or without bile duct excision) and 1785 bile duct pinch biopsies were reviewed. Twenty-three patients with a biliary adenoma were identified, arising either in the gallbladder (20/23) or the extrahepatic biliary tree (3/23). All gallbladder biliary adenomas were detected incidentally during cholecystectomy for unrelated indications.

Patient's medical records from the three patients with extrahepatic biliary adenomas were reviewed for demographic information, clinical pre-

sentation, imaging results, operative findings, and surgical pathology results. The study was approved by the institutional review board at Baystate Medical Center, Springfield, MA.
A literature review of published cases of extrahepatic biliary adenoma was performed using MEDLINE database. All identified cases were reviewed and the findings are summarized.

Results

Case 1

An 85-year-old woman with a history of atherosclerotic disease and gallstones was referred to the Gastroenterology outpatient office for evaluation of an incidental finding of biliary dilation up to 19 mm. The patient complained of intermittent abdominal pain but denied nausea, vomiting, jaundice, or weight loss. Her liver function tests (LFTs) were normal. Endoscopic ultrasound revealed a small soft-tissue non-shadowing lesion in the distal common bile duct (CBD) without evidence of a pancreatic head lesion (**Fig. 1**). Endoscopic retrograde cholangiopancreatography (ERCP) showed diffuse dilation of the biliary tree with a fixed filling defect in the distal CBD without focal stricture. Forceps biopsies revealed papillary and cribriform adenomatous epithelium with high grade dysplasia (**Fig. 2**). A biliary stent was not placed due to normal LFTs. The patient was deemed to be a poor surgical candidate for pancreaticoduodenectomy. Five months after initial presentation, the patient represented with jaundice, decreased appetite, weakness, and weight loss, with an obstructive pattern on her LFTs. ERCP showed a 15-mm occlusive stricture in the distal CBD with diffuse proximal biliary dilation; a metal stent was inserted. Brush cytology showed atypical ductal cells suspicious for adenocarcinoma. One year later, she was found to have duodenal ulceration from underlying cholangiocarcinoma with extensive liver metastases.

Case 2

A 61-year-old woman presented to the hospital with abdominal pain and weakness. She had a medical history of primary sclerosing cholangitis, and idiopathic thrombocytopenic purpura status post-splenectomy, and was on chronic immunosuppression. Laboratory evaluation revealed leukocytosis, and blood cultures returned extended spectrum, B-lactamase-producing *Escherichia coli*. MRI of the abdomen showed an irregular, polypoid lesion in the common hepatic duct (**Fig. 3**). Direct cholangioscopy with multiple biopsies revealed a villous adenoma with extensive high grade dysplasia. Complete endoscopic polypectomy was unsuccessful, therefore she underwent total bile duct resection and Roux-en-Y hepaticojejunostomy. One year after her initial presentation, she presented with left flank pain and back pain. Imaging revealed bone metastases to the L5-S1 vertebral bodies with biopsy showing adenocarcinoma of pancreaticobiliary origin, along with liver metastases and peritoneal carcinomatosis.

Case 3

A 78-year-old woman with a history of reflux esophagitis presented with symptoms suggestive of gallbladder pathology. She was found to have a polypoid bile duct lesion on intraoperative cholangiogram. ERCP showed an adenomatous polyp with high grade dysplasia involving the distal CBD. The patient underwent distal bile duct resection with choledochojejunostomy. Four years after surgery, she was found to have a large mass in the roux limb of the jejunum causing obstruction of the small bowel and invading the transverse colon. She underwent transverse colectomy, partial small-bowel resection, resection of the prior hepaticojejunostomy, and creation of a new hepaticojejunostomy. Final pathology showed adenocarcinoma. The patient underwent chemotherapy which was discontinued due to poor tolerance. Two years later, she was found to have metastatic disease to the liver, brain, and skin.

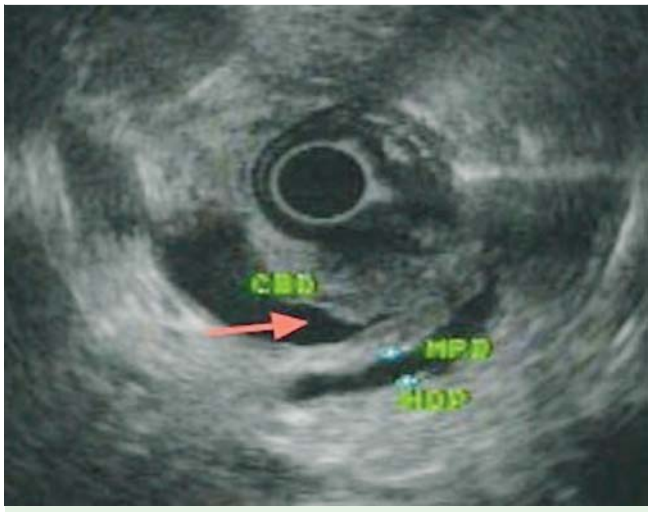

Fig. 1 Endoscopic ultrasound showing non-shadowing lesion in the CBD in the head of the pancreas.

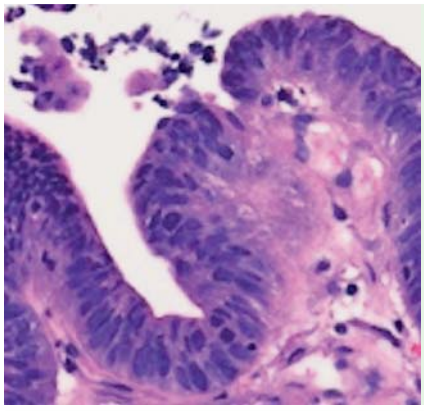

Fig. 2 Forceps biopsy showing adenomatous epithelium with high grade dysplasia.

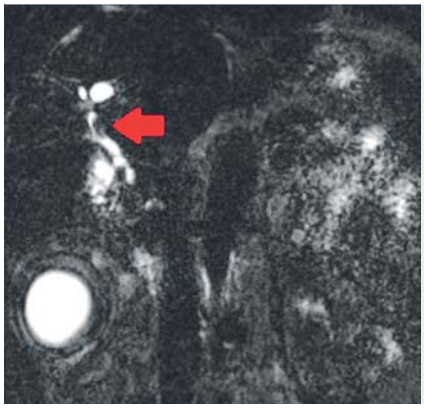

Fig. 3 MRI showing polypoid lesion in the common hepatic duct.

Table 1 Cases of extrahepatic biliary adenoma reported in the literature including their clinical presentation, histology, treatment, and outcome.

Reference	N	Gender	Age, years	Country	Location	Presentation	Treatment	Histology	Outcome
Ariche et al. [2]	1	F	77	Israel	Mid CBD	Recurrent abdominal pain, jaundice, fever	Local excision, roux-en-y hepatojejunostomy	Villous adenoma	–
Burhans and Myers [3]	1	F	64	USA	Left hepatic duct	Symptoms of cholecystitis, jaundice, fever	Removal with forceps surgically	Papillary adenoma	Presented 4 years later with large cystic mass. Alive at 5 years
	1	F	76	USA	CBD (junction of cystic and bile duct)	Jaundice, fever, anorexia, n/v	Curettage	Adenoma	Died 6 years later from CVA
Hultén et al. [4]	2	M	61	Sweden	Distal CBD	Biliary colic and jaundice	Local excision/choledochectomy and hepaticoduodenostomy	Papillary adenoma	Alive after 7 years
		M	80	Sweden	Distal CBD	Transient jaundice	Curettage/choledochoduodenostomy	Papillary adenoma	Returned 7 months later with adenocarcinoma
Shemesh [5]	1	M	58	Israel	Distal CBD	Recurrent abdominal pain	Surgically removed	Tubular adenoma	Well at 2 months
Sturgis et al. [6]	1	F	81	UK	Distal CBD	Intermittent right upper quadrant (RUQ) pain, nausea/vomiting	Endoscopic excision	Tubulovillous adenoma	Well post-surgery
Futami et al. [7]	1	F	40	Japan	Inferior bile duct	Relapsing pancreatitis	Surgical excision	Adenoma	Uneventful for 18 months
Jao et al. [8]	1	M	60	Taiwan	Distal CBD	Abdominal screening ultrasound	Endoscopic excision	Tubulovillous adenoma	Well at 2 months
Ibrarullah and Sreenivasa [9]	1	F	33	India	Distal CBD	RUQ pain, vomiting	Roux-en-y hepatojejunostomy	Adenoma	Asymptomatic at 38 months
Katsinelos et al. [10]	1	M	58	Greece	Distal CBD	Abdominal pain, jaundice, nausea/vomiting, RUQ mass	Whipple	Adenoma	Well at 6 months
Kim et al. [11]	1	M	55	Korea	Distal CBD	Painless jaundice and pruritis	Whipple	Tubulovillous adenoma	Multiple gastrointestinal polyps 8 months after surgery
Aparajita et al. [12]	1	F	75	UK	CBD (junction at cystic duct)	Jaundice, weight loss	Pancreaticoduodenectomy with Roux-en-Y reconstruction	Papillary adenoma	Well 9 months after surgery
Akaydin et al. [13]	1	M	60	Turkey	Proximal CBD	Painless jaundice, pruritis, acholic feces	Excision and Roux-en-Y hepaticojejunostomy	Tubulovillous adenoma	–
Munshi and Hassan [14]	1	F	69	USA	Distal CBD, junction at cystic duct	RUQ pain, pruritis, light stools	Endoscopic excision	Papillary adenoma	Surveillance with no symptoms, unclear interval
Prachayakul et al. [15]	1	M	53	Thailand	Distal CBD	Recurrent fever with intermittent jaundice	Polypectomy endoscopically	Tubular adenoma	Polyp disappeared on repeat procedure
Sirimontaporn et al. [16]	1	M	73	Thailand	Mid to distal CBD	Recurrent liver abscess/Klebsiella bacteremia	Endoscopic forceps biopsy	Adenoma	Further biopsy normal, no interventions afterwards
Styne et al. [17]	1	F	59	USA	Left hepatic duct	Recurrent cholangitis	Surgical excision	Papilloma	2 months later adenocarcinoma
Cardoza et al. [18]	1	F	53	USA	Common hepatic duct	Incidental LFT elevation	Surgical resection	Papilloma	–
Jennings et al. [19]	1	M	58	UK	Common hepatic duct	Jaundice	Surgically enucleated and stalk resected	Villous adenoma	16 months after presentation, recurrent villous adenoma, hepatic duct, roux-en-y
Colarian and Wescott [20]	1	F	78	USA	Common hepatic duct	Painless jaundice	Hepatojejunostomy	Villous adenoma	Recovered from surgery

Table 1 (Continuation)

Reference	N	Gender	Age, years	Country	Location	Presentation	Treatment	Histology	Outcome
Sotona et al. [21]	1	M	58	Czech Republic	Left hepatic duct	Painless obstructive jaundice	Local excision, Roux-en-Y hepaticojejunostomy	Papillary adenoma	Alive 1 year after the surgery
Ho and Lee [22]	1	M	15	Taiwan	Cystic duct	Tarry stools, jaundice	Exploratory laparotomy	Papillary adenoma	–
Loh et al. [23]	1	F	72	UK	Cystic duct	Recurrent RUQ pain, nausea	Surgical resection with cholecystectomy	Papillary adenoma	–
Liu et al. [24]	1	F	61	China	Cystic duct	Intermittent upper abdominal pain and fever	Snare polypectomy using a gastroscope	Tubulovillous adenoma	Asymptomatic at 3 months
O'Shea et al. [25]	1	M	75	USA	Left hepatic and common hepatic ducts	RUQ pain, jaundice, dark urine, weakness	Excision surgically	Villous adenoma	–
Morris-Stiff et al. [26]	1	F	73	UK	Common hepatic and proximal left hepatic duct	Abdominal pain, weight loss	Surgical resection, Roux-en-Y hepaticojejunostomy	Papillary adenoma	–
Hanafy and McDonald [27]	1	M	76	UK	CBD, hepatic and cystic duct	Mild jaundice and RUQ mass	Local excision surgically	Villous adenoma	–
Xu and Chen [28]	1	F	27	China	CBD and hepatic ducts	Painless jaundice and pruritis	Whipple/resection of extrahepatic bile duct and whipple	Villous adenoma	Well 9 months after surgery
Saxe et al. [29]	1	M	64	USA	Distal CBD	Recurrent abdominal pain, jaundice, weight loss, pruritis	Whipple	Villous adenoma	Well at 3 years
Blot et al. [30]	1	M	84	France	Distal CBD	Febrile jaundice	Surgical excision	Villous adenoma	Well at 1 year
Inagaki et al. [31]	1	M	73	Japan	Distal CBD	Epigastric pain and jaundice	Whipple	Papillary adenoma	Well at 12 months after surgery
Chang et al. [32]	1	M	51	Taiwan	Distal CBD	Febrile jaundice, RUQ pain	Refused surgery	Papillary adenoma	Asymptomatic after 3 months
Aggarwal et al. [33]	1	M	55	India	Mid CBD	Recurrent abdominal pain	Whipple	Adenoma	–
Lou et al. [34]	1	M	47	Taiwan	Distal CBD	Fever, abdominal pain	Local excision surgically	Tubular adenoma	Well at 8 months
Fletcher et al. [35]	1	M	74	UK	Distal CBD	Painless jaundice, pruritis, weight loss	Whipple	Papillary adenoma	Well at 1 year after surgery
Present cases	3	F	85	USA	Distal CBD	Abdominal pain	Refused surgery	Papillary adenoma	Cholangiocarcinoma 5 months after presentation
		F	78	USA	Distal CBD	Gallbladder symptoms	Distal bile duct resection with choledochojejunostomy	Adenoma	Adenocarcinoma involving small/large bowel 4 years after surgery
		F	61	USA	Common hepatic duct	Febrile bacteremia	Local excision unsuccessful; total, subsequent bile duct resection and Roux-en-y hepaticojejunostomy	Villous adenoma	Metastases to the bone 1 year after initial presentation

CBD, common bile duct; CVA, cerebrovascular accident; LFT, liver function test; RUQ, right upper quadrant.

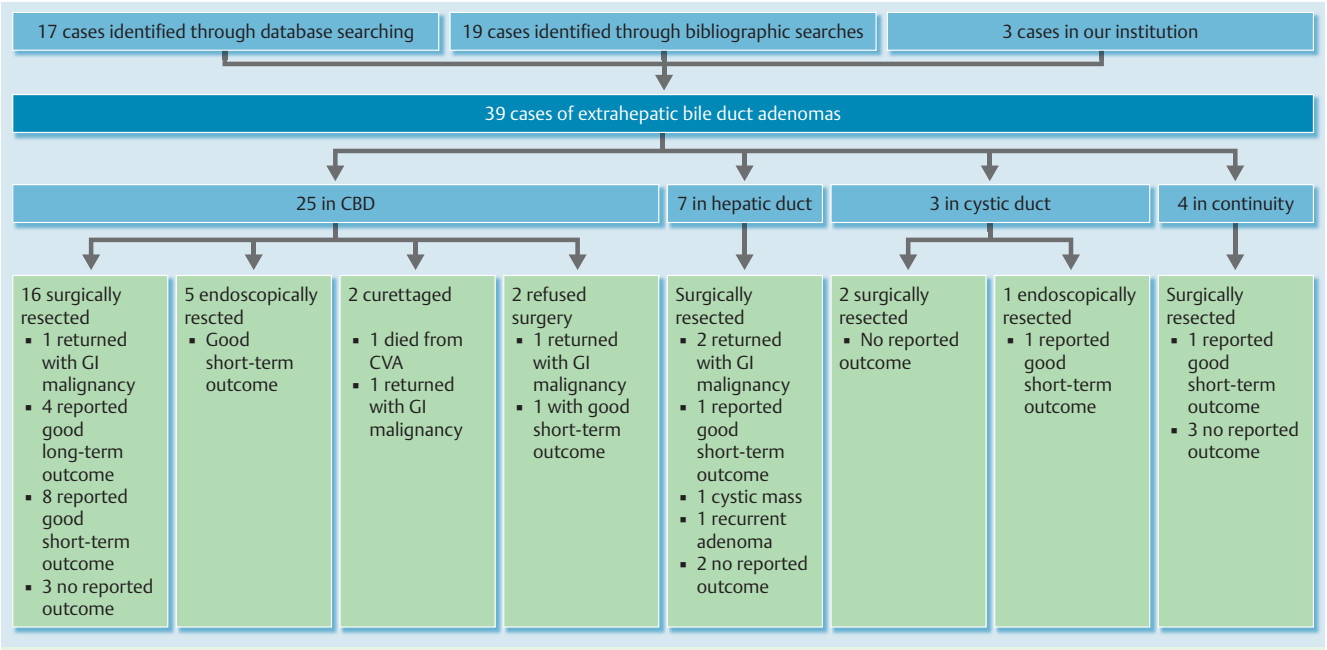

Fig. 4 Flow chart summarizing all 39 reported cases of extrahepatic biliary adenoma.

Discussion

Benign tumors of the extrahepatic biliary tree can be divided into epithelial and non-epithelial tumors. There is little uniformity in the nomenclature applied to benign epithelial lesions and various classifications have been proposed. According to the WHO classification, they are divided into five different types: tubular, papillary (also known as papillomas), tubulopapillary, biliary cystadenoma, and papillomatosis [1]. Adenomas comprise two-thirds of benign biliary tumors [2]. For the purpose of this review, we have focused on adenomas involving the extrahepatic bile duct, excluding ampullary adenomas, cystadenomas, and papillomatosis. Three extrahepatic bile duct adenomas were diagnosed at our institution among a total of 10 559 bile duct pinch biopsies and surgical specimens (0.03 %) over 13 years. One of our cases has been reported previously [1]. On extensive review of the literature, we found another 36 cases making a total of 39 cases of extrahepatic biliary adenomas reported to date [2 – 28] (**Table1** and **Fig. 4**).

Demographics and presentation

Extrahepatic biliary adenoma appears to be a disease of older patients. The age of presentation ranged from 15 to 85 years with a mean age of 62.8 ± 15.4 years (male, 61.0 ± 14.4 years; female, 64.6 ± 16.3 years). The affected gender was male in 21 cases [4, 5, 8, 10, 11, 13, 15, 16, 19, 21, 25, 27] and female in 18 cases [2, 3, 6, 7, 9, 12, 14, 17, 18, 20, 23, 24, 26, 27]. The most common presenting complaints were abdominal pain, jaundice, fever, pruritus, and abnormal LFTs. One of our cases presented with recurrent bacteremia in the setting of underlying primary sclerosing cholangitis. Two reported cases were asymptomatic with incidental findings of biliary dilation on imaging [1, 8]. One case was found incidentally in a surgical resection specimen performed for duodenal adenocarcinoma [11].

Histology

The pathology specimen was obtained surgically in 32 cases and endoscopically in seven cases. In 22 cases, the adenomas were associated with atypia/dysplasia. The location of adenomas was in the CBD (25/39; 64 %) [2 – 16], common hepatic duct (7/39; 18 %) [3, 17 – 24], and cystic duct (3 /39; 8 %) [22 – 24]. Four (10 %) cases involved multiple ducts in continuity [25 – 28].

Treatment

Management of extrahepatic bile duct adenomas is not clearly defined. Surgical resection was the primary mode of therapy in 31 of 39 patients [2 – 5, 7, 9 – 13, 17 – 23, 25 – 28]. Cases in the 1970 s have reported using limited surgical curettage without resection of the affected area [3, 5]. Endoscopic resection with snare polypectomy or forceps has been reported in six cases [6, 8, 14 – 16, 24]. There are no reports of the use of ablative therapy with radiofrequency ablation or photodynamic therapy after endoscopic resection.

Prognosis

The follow-up period varied among all the cases reported. The majority of the patients had good short-term outcomes. Long-term follow-up (>1 year) and short-term outcome (<1 year) were reported in 8 [3, 7, 11, 19] and 17 cases [4, 5, 8, 10, 11, 15 – 17, 21, 24, 28], respectively. Five cases presented with interval malignancy including cholangiocarcinoma, and small-bowel adenocarcinoma was noted at follow-up [1, 4, 17]. The longest follow-up was reported to be 7 years with the patient still alive [4]. Associations were found with certain malignancies and syndromes either at presentation or follow-up, including Gardner's syndrome, familial polyposis coli, or periampullary carcinoma [5, 7, 12].

Conclusion

We highlight the rarity of extrahepatic bile duct adenoma with three additional cases from our institution adding to the paucity of literature on the subject. All three patients in our series presented with subsequent biliary malignancy with metastases or local invasion. We recommend aggressive surgical intervention and close postoperative surveillance when diagnosis of extrahepatic bile duct adenoma is made.

Competing interests: None

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